REMARKS

Prior to entry of the present amendment, claims 1-19 are pending in the application. Claims 1-7 and 9-19 are rejected under 35 U.S.C. § 112, first paragraph, for lack of enablement. Claims 1-19 are rejected under 35 U.S.C. § 103 as being unpatentable over Larsen et al. (U.S. Patent Application Publication No. 2001/0008625; hereafter "Larsen '625") in view of Larsen et al. (WO 02/05859; hereafter "Larsen '859") and Goldenberg (U.S. Patent No. 6,083,477; hereafter "Goldenberg"). Claims 1-9, 18, and 19 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting over claims 1, 2, 4, 6, 7, 9-11, 14, and 15 of co-pending U.S. Patent Application Serial No. 10/421,244 (hereafter "the '244 application"). The abstract is objected to for containing improper language, and claim 19 is objected to for lacking correct punctuation. Applicants address each basis for rejection and objection below.

Claim Amendments

Claims 1-13, 18, and 19 have been cancelled. Claim 15 has been amended to correct a minor typographical error. No new matter has been added by the present amendments. Applicants reserve the right to pursue any cancelled subject matter in this or in a continuing application.

Objections

The Office objects to the Abstract for containing "legal phraseology" (Office Action, page 2). Applicants submit that the Abstract as amended is free of this basis for objection. The objection to the Abstract may be withdrawn.

The Office objects to claim 19 for lacking correct punctuation (Office Action, page 2). As claim 19 has been cancelled, this objection is moot.

Rejection under 35 U.S.C. § 112, First Paragraph

Claims 1-7 and 9-19 are rejected under 35 U.S.C. § 112, first paragraph, for lack of enablement. As claims 1-7, 18, and 19 have been cancelled, the rejection as applied to these claims is moot. With respect to the remaining claims, Applicants respectfully traverse the enablement rejection.

The Office states that, while the specification is enabling "for the diseases listed in...instant claim 8, [it] does not reasonably provide enablement for all soft tissue disease[s]" (Office Action, page 2). As the basis for this conclusion, the Office states that "[v]arious soft tissue diseases having various different causes are not treatable by a single composition" (Office Action, page 3), that "[t]he specification provides no direction for ascertaining, *a priori*, which soft tissue diseases can be treated, except those listed in the instant claim 8" (Office Action, page 5), and that "Applicants fail to provide the guidance and information required to ascertain how the treatment of all soft tissue diseases will be effective without resorting to undue experimentation" (Office Action, page 5). Applicants respectfully disagree.

Pending claims 14-16 are directed to pharmaceutical compositions containing a soft tissue targeting complex of thorium-227 and a complexing agent, where the thorium-227 is conjugated to a targeting moiety with bioaffinity (excluding bone-seekers, liposomes, and folate-conjugated antibodies or antibody fragments). Claim 17 is directed to methods of generating such pharmaceutical compositions. The Office appears base the rejection of claims 14-17 on the breadth of diseases encompassed by the term "soft tissue disease," rather than on the term "soft tissue targeting complex," as recited in claims 14-17.

Applicants submit that one skilled in the art would recognize what is meant by the term "soft tissue targeting complex" and would recognize the types of complexes encompassed by this term. In addition, Applicants submit that the teaching and examples in the specification provide one skilled in the art with sufficient information to make and

use the claimed compositions, and to test the ability of the compositions to target soft tissue at the time of filing. The teaching in the specific Examples of the specification are applicable to the full scope of compositions encompassed by claims 14-17.

Applicants' specification describes soft tissue targeting compositions that contain a complex of thorium-227 and a complexing agent, where thorium-227 is conjugated to a targeting moiety with bioaffinity. Examples of such targeting moieties are provided at page 10, lines 10-25 of the specification as filed. Applicants have discovered that soft tissue targeting compositions containing thorium-227 are valuable therapeutics. In view of Applicants' discovery, thorium-227 can be implemented in a variety of soft tissue targeting compositions; however, it would be impractical for Applicants to provide a working example of every possible type of soft tissue targeting complex falling within the scope of claims 14-17. Applicants note that the specification, to meet the enablement requirement under 35 U.S.C. § 112, first paragraph, need not describe examples of each and every compound encompassed by the claims, but rather must teach the skilled artisan how to make and use the invention encompassed by the claims without undue experimentation. Applicant's specification meets this standard. The methods taught in the specification, in combination with the knowledge in the art, may be applied to make and use the compositions encompassed by claims 14-17 without undue experimentation. Applicants submit that the enablement rejection of claims 14-17 under 35 U.S.C. § 112, first paragraph may be withdrawn.

Rejection under 35 U.S.C. § 103

Claims 1-19 are rejected under 35 U.S.C. § 103 as being unpatentable over Larsen '625 in view of Larsen '859 and Goldenberg. As claims 1-13, 18, and 19 are cancelled, the rejection of these claims is moot.

In making the obviousness rejection, the Office states that Larsen '625 teaches a "receptor binding conjugate [that] comprises an antibody, radionuclide (i.e., ^{227}Th or

^{223}Ra, etc.) and a folate (derivative)…" (Office Action, page 6). The Office further states that Larsen '859 discloses the "method of treating a malignant soft-tissue disease by administering to a mammalian subject a ^{227}Th-chelator radiopharmaceutical complexes" (Office Action, page 6; citations omitted), that the contemplated treatment includes "soft tissues" (Office Action, page 7), and that "[t]he decay of the ^{227}Th generates in vivo an emissions cascade of α-particles, such as the daughter radionuclide ^{223}Ra that will occur in the target area…" (Office Action, page 6). The Office further relies on Goldenberg for teaching a "toxin-therapeutic radionuclide complex which effectively localizes to a desired cancer site…" and that "doses of antibody and/or radioactivity usually require stem cell rescue" (Office Action, pages 7 and 8). The Office concludes that "it would have been obvious to one ordinarily skill in the art to utilize a soft-tissue…targeting radionuclide complex, such as one taught by…[Larsen '625] with the doses of…[Larsen '859] to reduce myelotoxicity" (Office Action, page 8). Applicants respectfully traverse this basis for rejection.

Larsen '625 discloses receptor binding conjugates which are directed to, or against, the folate receptor expressed on tumors expressing a folate-binding protein. Larsen '625 describes such folate derivatives (conjugates) and the preparation of such conjugates. The conjugates described in Larsen '625 are not encompassed by claims 14-17 because folate conjugates are specifically excluded from the claimed subject matter. As indicated above, Larsen '625 describes the use of *folates*, with thorium-227 given as just one of a number of possible isotopes which could be delivered. There is no teaching or suggestion that thorium-227 is specifically suitable for any particular application (e.g., for targeting to soft tissues), nor is there any teaching of a therapeutic window (dosage range) for thorium-227 in soft tissues.

Applicants' specification, at page 6, lines 19-24 states:

> ^{227}Th that has progenies emitting four alphas [alpha particles], all preceded by the 11.4 day half-life of the ^{223}Ra daughter is likely to cause almost complete translocalization of the progenies compared to the mother ^{227}Th

> nuclide and thus considerable difficulties in controlling the site of these four alpha emissions and as a result a high likelihood of unwanted side effects.

This statement in the specification reflects the state of the art as of the priority date of the present application. Nothing in Larsen '625 counters the general understanding in the art prior to the filing date that the daughter radionuclide of thorium-227 (^{223}Ra) is too toxic in soft tissue to allow for the creation and successful use of pharmaceutical soft tissue targeting complexes of thorium-227, as recited in claims 14-17.

Larsen '859 describes the use of thorium-227 for use in bone targeting complexes. The thorium conjugate described utilizes a *bone targeting* bisphosphonate which specifically binds to the hydroxyapatite mineral component of bone. Hydroxyapatite is not found in soft tissues, thus this conjugate would be ineffective in targeting soft tissues and hence, the complexes disclosed in Larsen '859 cannot be considered to teach towards compositions which are "soft tissue targeting," as required by claims 14-17.

Applicants further note that the doses recited in Larsen '859, and relied on by the Office, are not specific to thorium-227, but are specific to a method in which the isotope is targeted to bone. There will inevitably be some material which reaches the soft tissue, but that is in no way comparable to providing the same treatment *specifically* to a soft tissue site. There are no "soft tissue targeting" complexes taught in Larsen '859 because, in all cases, the complexes are described as being "bone targeting." The table on page 15 of Larsen '859 shows that for thorium-227, specifically, ten times as much radiolabel reaches the bone in comparison with soft tissue sites, and that less than 5% of the administered dose is found in soft tissue. The teaching of Larsen '859 with respect to dosages provides no information with regard to the dosages that are tolerable in soft tissue. Furthermore, the existence of a therapeutic window (dosage range), where the isotope is targeted to bone and the daughter localized by bone incorporation, does not reflect upon a corresponding therapeutic window in soft tissue.

The reason that thorium-227 can be used at the dosages disclosed in Larsen '859 is set forth in the paragraph spanning the second half of page 5. This paragraph explains that thorium-227 and actinium-225 can be incorporated into bone using chelates which *clear rapidly* from soft tissues. The result of this is that "[a]lpha cascade emitter series originating from, for example, actinium-225 and thorium-227, can thus be incorporated into bone surfaces and used to treat bone surfaces and osseous tumors..." (page 5, lines 30-33). This is a key point: bone-seeking thorium and actinium chelates can cause incorporation into bone so that the whole decay cascade occurs *within the calcified tissue* at the bone surface, thus preventing the daughter isotopes from causing toxicity. Larsen '859 provides no further teaching or suggestion for the use of thorium-227. Bone-seeking chelates designed to promote incorporation into bone cannot be seen as either teaching or suggesting "soft tissue targeting" compositions.

Further, the dose ranges in Larsen '859, if applied to thorium-227 in soft tissues span all the way from therapeutically inactive to unquestionably lethal. This general dosage range provides no useful information to the skilled artisan, because these same effects can be achieved by any arbitrary minimal or maximal dose. These doses therefore do not render it obvious to provide *soft-tissue targeting* compositions of thorium-227, because these are directly taught away from in this reference (as the compositions target bone), and are not even indirectly suggested by any accidental disclosure of a therapeutic window or dose. Prior to Applicants' discovery, no therapeutic window for thorium-227 in soft tissue was known to exist. Larsen '859 contains no teaching that would suggest that the complexes of the type encompassed by claims 14-17 are capable of therapeutic application in soft tissue.

The third cited reference, Goldenberg, fails to remedy the deficiency of Larsen '625 and Larsen '859 because Goldenberg also provides no teaching or suggestion of a dosage of thorium-227 therapeutically useful in a soft-tissue targeting complex. The Office uses Goldenberg as a basis for asserting that stem cell therapy (as recited in claim

10) is obvious. Claim 10 has been cancelled and the presently pending claims are directed to compositions of matter requiring a particular dosage of thorium-227 and methods of making the claimed compositions of matter. Applicants submit that the teachings of Goldenberg, even if combined with the other cited references, cannot render claims 14-17 obvious.

In sum, Applicants submit that there is no teaching or suggestion in the combination of Larsen '625, Larsen '859, and Goldenberg that would lead one skilled in the art to arrive at the invention encompassed by claims 14-17. The cited documents, even if combined, fail to teach or suggest that a therapeutically effective soft *tissue-targeting complex* of thorium-227 could be made. There was also no reasonable expectation of success in generating such a complex, because none of the cited documents teaches that complexes of this type could be both useful and non-toxic when targeted to soft-tissue. The state of the art at the time of filing, as discussed above and summarized in the specification as filed, indicated that a therapeutic window could only exist by targeting thorium-227 to calcified tissue. For these reasons, Applicants submit that the rejection of claims 14-17 under 35 U.S.C. § 103 should be withdrawn.

Provisional Nonstatutory Obviousness-Type Double Patenting Rejection

Claims 1-9, 18, and 19 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting over claims 1, 2, 4, 6, 7, 9-11, 14, and 15 of the '244 application. As claims 1-9, 18, and 19 have been cancelled, Applicants submit that this provisional rejection is moot.

CONCLUSION

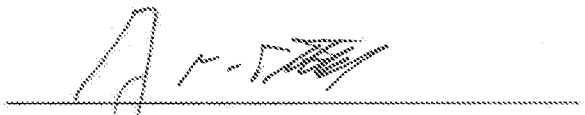
Applicants submit that the claims are in condition for allowance and such action is hereby respectfully requested.

Transmitted herewith is a Petition to extend the period for replying to the Office Action for three months, to and including March 10, 2010, and payment of the required extension fee.

If there are any additional charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

Date: 10 March, 2010



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